Non-aqueous Compositions for Treatment of Orthopedic Defects and Delivery of Bioactive Agents

FIELD OF THE INVENTION

This invention relates to non-aqueous compositions for drug delivery and which can take the place of bone.

BACKGROUND OF THE INVENTION

Cements based on calcium sulfate and calcium phosphate are used in orthopedic procedures as bone graft substitutes and drug delivery matrices. See Damien, C, et al., Bone Graft and bone graft substitutes, J. Orthop. Trauma 5:1-8 (1991); Bahn, S, Plaster: A bone substitute, Oral Surg. Oral Med. & Oral Path. 21:672-681(1966); Hulbert, SF, et al., History of Bioceramics, Ceramics Internat., 131-140(1982); Mackey D, et al., Antibiotic loaded plaster of Paris pellets, Clin. Orthop. Rel. Res.,167:263-268(1982); Royer US Patents 6,391,336; 6,497,901; 6,639,486; Brown WE and Chow LC, A new calcium phosphate setting cement, J. Dent. Res. 62:672-679(1983); Driessens, FCM, Boltung, MG, and Wenz R, Calcium Phosphate Bone Cements:State of the Art 2000, 12th Conf. of the Eur. Soc. Biomech., August 2000; Ooms EM, et al., Trabecular Bone Response to Injectable Calcium Phosphate Cement, J. Biomed. Mater. Res. 61:9-18(2002); Constanz, BR, et al., Skeletal Repair by in Situ Formation of the Mineral Phase of Bone, Science, 267:1796-1799; and Fulmer, et al., US Patent 5,571,493. Calcium salts in the form of powders are mixed with water to form a slurry, which in some cases, is injectable. Other preparations resemble paste or dough. See Chow, LC and Takagi, US 2002/0137812A1.

Calcium sulfate hemihydrate reacts with water and forms a solid as follows:

$$CaSO_4\text{-hemihydrate} + H_2O \rightarrow CaSO_4\text{-dihydrate}\downarrow \qquad (1)$$

The solubility of the hemihydrate is higher than the dihydrate product, which precipitates as needle-like, interlocking crystals to form a porous solid as the hydration reaction occurs. Phosphate cements usually involve the formation of apatitic crystals (some form of $Ca_5(PO_4)_3OH$). There are two basic types of aqueous phosphate cements, which contain either alpha tricalcium phosphate (aTCP) or tetracalcium phosphate (TTCP). aTCP cements are formed as shown in reaction (2)

$$Ca_3(PO_4)_2 + 2CaHPO_4 + 2Na_2HPO4(aq) \rightarrow Ca_5(PO_4)_3OH + \text{Other phosphates} \qquad (2)$$

These formulations usually contain hydroxyapatite (HA) seed crystals; aqueous sodium phosphate serves as an accelerator. Calcium carbonate is sometimes included in these cements. See Khairoun, I, et al., Effect of Calcium Carbonate on Clinical Compliance of Apatitic Calcium Phosphate Bone Cement, J. Biomed. Mater. Res, 38:356-360(1997).

TTCP cements involve a hydration/polymerization as shown in reaction (3):

$$Ca_4(PO_4)_2O + CaHPO_4 + H_2O \rightarrow Ca_5(PO_4)_3OH \text{ (HA)} \quad (3)$$

Other formulations produce calcium deficient HA or amorphous calcium phosphate having undefined stoichiometry.

The cements that are currently in commercial use are prepared by mixing a powder and an aqueous liquid just prior to application. Some cements require a machine to effect adequate, uniform mixing. The time and technique used for hand mixing are sources of variation. Deviation from prescribed procedures can lead to malfunction of the product.

OBJECTS OF THE INVENTION

It is an object of the invention to provide inorganic based cements that meet performance criteria such as compressive strength, setting time, and cohesion. Generally, it is desirable to have a compressive strength of 30 mega Pascals (MPa), which is 2-6 times that of human cancellous bone.

It is an object of the invention to provide a setting time of 15 minutes or less which is desirable in many orthopedic procedures. Cohesion is important in that movement/dispersion of the cement after contacting body fluids, soft tissue, or bone is often problematic.

It is an object of the invention to provide a system to deliver bioactive agents. Antibiotics, local anesthetics, anti-tumor agents and osteogenic factors are examples of bioactive agents that are of interest.

It is an object of the invention to provide a bone cement which requires no mixing prior to application.

SUMMARY OF THE INVENTION

The subject non-aqueous, ready-to-use composition is comprised of the following:

- an inorganic salt or salts capable of hydration and precipitation, such as calcium sulfate or calcium phosphate salt or mixtures thereof,
- an organic polymer such as ethyl cellulose, and
- a non-aqueous solvent such as N-methylpyrrolidone.

In another embodiment, demineralized bone matrix is used in place of some or all of the inorganic salt.

Optionally, the composition also includes a bioactive agent, an accelerator or retarder, and/or a porosogenic agent. The invention also includes syringes containing the composition of the invention, and a prosthesis or in-dwelling medical device coated with the composition.

The compositions are useful for drug delivery and/or as bone substitutes.

The invention also includes a method of treating osseous defects in a mammal comprising administering by injection a liquid inorganic based non-aqueous composition to the defect wherein the composition hardens to a solid after injection. The amount of the composition used is that sufficient to treat, fill, or reduce the size of, the defect.

The invention includes a method of producing sustained release of an active agent in a mammal comprising administering by injection to the mammal a non-aqueous liquid composition containing the active agent, wherein the composition hardens to a solid after injection. The invention also includes method of producing sustained release of an active agent in a mammal comprising administering to said mammal a composition comprising:

an active agent,

an inorganic salt capable of hydration and precipitation,

an organic polymer, and

a non-aqueous solvent.

The invention also includes a method of producing a non-aqueous composition for sustained release of a bioactive agent comprising the steps of:

a) mixing an inorganic salt capable of hydration and precipitation with a bioactive agent,

b) preparing a non-aqueous polymer solution using an organic soluble polymer and a non-aqueous solvent, and

c) blending the product of step a) with the non-aqueous polymer solution.

The invention also includes a syringe containing, or prosthesis or in-dwelling medical device coated with, the composition of the invention.

Another aspect of the invention is a kit comprising a first compartment containing a powder comprised of calcium phosphate or calcium sulfate, a drug and optionally a porosogenic agent; and a second compartment containing a liquid non-aqueous solution comprised of an organic polymer and a solvent for the polymer. When mixed, the powder and liquid non-aqueous solution form an injectable suspension which hardens to a solid after exposure to an aqueous environment. Preferably, each of the first and second compartments is

a syringe connectable to one another to allow the powder and liquid non-aqueous solution thereof to be transferred between the syringes.

The invention also is embodied in a method of administering an injectable non-aqueous liquid composition to a mammalian patient, comprising providing a kit as described immediately above, mixing the powder and the liquid non-aqueous solution to form an injectable suspension, injecting the injectable suspension into a mammalian patient at a desired anatomical site, and thereafter allowing the injectable solution to harden to a solid at the site. Most preferably, the first and second compartments comprise respective syringes connectable to one another to allow the powder and liquid non-aqueous solution thereof to be transferred therebetween, such that mixing the powder and liquid non-aqueous solution comprises fluid-connecting the syringes and then repeatedly transferring the powder and liquid non-aqueous solution between the syringes for a time sufficient to form the injectable suspension.

DETAILED DESCRIPTION OF THE INVENTION

A. Compositions of the Invention

The compositions of the subject invention are suspensions of an inorganic, e.g. calcium salt or salts in a non-aqueous polymer solution. The product can be loaded into a syringe. When contacted with an aqueous environment, the composition sets. As the non-aqueous solvent diffuses away and is replaced by water, the inorganic salt or salts are hydrated which leads to solidification.

The subject invention is a ready-to-use bone void filler and bone graft substitute. The composition can be used for structural purposes, dead space management, and/or delivery of bioactive agents. The formulations described herein require no mixing or other preparation at tableside by the surgeon. The mixture of non-aqueous solvent, organic polymer, and calcium salts is provided in a ready-to-use syringe or other package.

The components include inorganic salts capable of hydration and precipitation, one or more polymers, a non-aqueous solvent; optional components include bioactive agents, accelerators, retarders, complexing agents, porosogenic agents, and drug release modifying agents. In one embodiment, compositions of the invention provide a setting time of 15 minutes or less which is desirable in many orthopedic procedures. In another embodiment, the composition sets instantly, i.e. in less than 5 seconds. In an advantageous embodiment, the composition forms a solid having a compressive strength of at least 30 mega Pascals (MPa).

The compositions provide good cohesion and allow control of porosity, resorption rate, and sustained drug release profile. The compositions can release the active agent for days (e.g.1-7 days) or weeks (e.g.1-6 weeks) depending on the components selected.

The compositions of the invention are typically manufactured as follows:

- preparing a non-aqueous polymer solution using an organic soluble polymer and a non-aqueous solvent. An example is ethyl cellulose dissolved in dry NMP at a concentration of 6% (w/v).
- blending a dry inorganic salt component with the non-aqueous polymer solution. The inorganic salts are optionally mixed with a bioactive substance. An advantageous ratio of dry powder to liquid is 1/0.6. The range is approximately 1/1 to 1/0.4. The powder/liquid ratio determines the injectability of the product. Suspensions containing relatively high levels of liquid are less stable, that is, settling can occur.

The suspension can be loaded into syringes. The syringes can be sterilized using gamma irradiation.

Following injection in the body, the solvent is exchanged for water, which leads to two events. First, the polymer quickly sets. Second, the incoming water reacts with the calcium salts to form a solid cement. Porosity is controlled by inclusion of $Ca(H_2PO_4)_2$ and $NaHCO_3$, which react with water to release carbon dioxide. The escape of carbon dioxide creates pores, which enhances the transformation of the synthetic cement to natural bone by admitting osteoclasts and osteoblasts, the cells responsible for remodeling of bone.

- **Inorganic Salt**

Salts of calcium must undergo hydration and solidification (Table 1). Advantageous salts are calcium sulfate hemihydrate and calcium phosphates. The calcium phosphate salts and calcium phosphate mixtures described above under the Background of the Invention can be the inorganic salt of the invention. Other salts such as aluminates and silicates can be used. Zinc based cements can also be employed. See Anusavich, KJ, Chapter 24, Phillips Science of Dental Materials, WB Saunders (1996) hereby incorporated by reference. Advantageously, the resulting solid is resorbable and, when appropriate, replaced by new bone. The salts and resulting solids should be non-toxic and have non-toxic breakdown products. Typically, a mixture of salts is used in a composition of the invention. Sterilization of the salts is possible with gamma irradiation or dry heat.

Table 1. Inorganic Salts-selection criteria and examples

Criteria for Selection

-Capable of undergoing isothermic hydration and precipitation

-Solid in 10-20 minutes

-Resorbable

-Safe, non-toxic to local tissues and bone

-Sterilizable by dry heat or gamma irradiation

Examples

-Calcium sulfate-hh

-Tetracalcium phosphate

-Alpha tricalcium phosphate

-Beta tricalcium phosphate

The use of calcium phosphateas the inorganic optionally includes calcium hydrogen phosphate and/or disodium hydrogen phosphate. For example, a calcium phosphate mixture can include aTCP, $CaHPO_4$,$CaCO_3$, hydroxyapatite, and Na_2HPO_4. Phosphate cements usually involve the formation of apatitic crystals (some form of $Ca_5(PO_4)_3OH$). These formulations usually contain hydroxyapatite (HA) seed crystals; aqueous sodium phosphate can serve as an accelerator. Calcium carbonate is optionally included in these cements.

- **Organic Polymer**

Criteria for selection of the polymer are shown in Table 2. The polymer should have relatively low solubility in water. The polymer should be soluble in the non-aqueous solvent of choice. As the non-aqueous solvent diffuses out and the water diffuses into the matrix, it is desirable to have rapid, isothermic setting of the composite, which is inversely related to the water solubility of the polymer. The polymer should be non-toxic to bone and soft tissue. The breakdown of the polymer should not result in the production of acid, which has a deleterious effect on bone healing. Polylactate esters are therefore less desirable because of the lactic acid produced as they degrade. The polymer should be otherwise pharmaceutically acceptable and be approved by FDA for use in parenteral products.

Polymer concentrations are kept low so that the hydration/precipitation reaction is not inhibited. In general the polymer should be present at levels between 1 and 10% of the solvent w/v. The advantageous level is between 3 and 6% of solvent. The nature and concentration of the polymer can be adjusted to affect the release profile of the bioactive agent.

Table 2. Organic Polymers-selection criteria and examples

Criteria for Selection

-Organic soluble

-Precipitable or gelable with water

-Biocompatible, safe

-FDA approved/approvable

-Bioerodible without acid production

Examples

-Ethyl cellulose

-Ethyl, ethoxyethyl cellulose

-Cellulose acetate

-Cellulose acetate, butyrate

-Dextran (acyl, alkyl)

-Other organic polysaccharides, polyamides, urethanes, and other pharmaceutically acceptable polymers that meet the criteria listed above.

- **Non-aqueous Solvent**

The non-aqueous solvents should be biocompatible and non-irritating to bone and soft tissue. The diffusivity should be high and the viscosity should be low. As an example glycerol is viscous and a poor choice. The resulting formulation is too thick and the setting reaction of the cement is slow. The solvent should readily dissolve the polymer of choice without heating, dialysis, etc. The solvent should be neutral, that is, not acidic or basic. The solvent should not be strongly nucleophilic or electrophilic. Halogenated and aromatic compounds are not preferred. The FDA Guidance of November 2003 lists solvents according to permitted daily exposure. Acceptable solvents for use in the subject invention are all class 3 or class 2 in the FDA Guidance (Table 3). Mixtures of acceptable solvents are also useful.

Table 3. Solvents-selection criteria and examples

Criteria for Selection

-Low toxicity

-Pharmaceutically acceptable

-Good solvent power

-Low viscosity (less viscous than glycerol)

-High diffusivity

-Neutral

-Non-reactive

Examples

-N-methylpyrrolidone

-Dimethylformamide

-Dimethylacetamide

-Dimethylsulfoxide

-Cyclohexane

-Methylcyclohexane

-Tetrahydrofuran

-Butyl acetate

-Ethyl acetate

-Ethyl formate

-Isopropyl acetate

-Propyl acetate

-Isobutyl acetate

- **Porosogenic Reagents and other Additives**

Incorporation of reagents that generate carbon dioxide will increase porosity. Advantageous reagents are adipic acid plus $NaHCO_3$, other organic acids (citric, tartaric, lactic, etc.), and $NH_3Al(SO_4)_2$, can be used in place of adipic acid. An alternative approach to producing a porous matrix is to include water-soluble crystals of innocuous compounds such as sugars, for example, sucrose, fructose and the like.

Addition of matrix polymers and complexing agents can be used to control the release of bioactive agent. See commonly owned US patents 6,391,336; 6,497,901; 6,639,486 hereby incorporated by reference in their entirety.

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Representative compositions are shown in Table 4.

Table 4. Representative Compositions of Non-aqueous Cements

Calcium Salt	Polymer Solution	Porosogen

$CaSO_4$-hh (1g)	6% EtC/NMP (600ul)	-----
CP Mixture (1g)	6% EtC/NMP (600ul)	-----
$CaSO_4$-hh (900mg)	6% EtC/NMP (600ul)	EF Mixture (100mg)
CP Mixture (850mg)	6% EtC/NMP (600ul)	EF Mixture (150mg)
CP Mixture (1g) + 50mg enrofloxacin	6% EtC/NMP (600ul)	-----
CP Mixture (1g)	6% CA/NMP (600ul)	-----

-CP = calcium phosphate mixture which includes aTCP(60%), $CaHPO_4$(25%), $CaCO_3$(9)%), HA(2%), and Na_2HPO_4(4%)

-6%EtC/NMP = 6% Ethyl cellulose (Sigma Chemical product number E-8003) in dry N-methylpyrrolidone (w/v).

-EF mixture = 3.7g adipic acid + 4.2g $NaHCO_3$

-CA = cellulose acetate

B. Uses and Modes of Administration of the Compositions of the Invention

The non-aqueous compositions of the invention are well suited for use as a bone substitute, e.g. as a bone void filler, and/or for the sustained delivery of a wide variety of bioactive agents. In an advantageous embodiment, the compositions of the invention are injectable.

Orthopedic treatments (no medicinal)

The subject compositions can be used advantageously as synthetic bone substitutes. Filling of osseous defects, which results from disease or trauma is a general use of bone substitutes. Use in conjunction with fracture repair is important, especially in distal radius and proximal tibia fractures. Other uses include dead-space management, spine fusion, kyphoplasty, maxillofacial/cranial surgery, filling of periodontal defects, and dental uses. Useful additives or combination ingredients include dimineralized bone matrix, allograft bone, and autograft bone.

Installation can be affected using a syringe directly or a syringe fitted with a cannula or needle, usually 18 –21gauge.

Orthopedic treatments (with medicinal)

Examples of treatment of osseous defects with delivery of medicinal include the uses noted above (where the is no medicinal) plus:

- delivery of osteogenic factors,
- intratumoral delivery of anti-neoplastic agents,
- filling of a void with the composition of the invention that contains cis-platin or other anti-neoplastic agent following removal of an osteosarcoma,
- filling a periodontal defect with the subject composition containing an antibiotic such as doxycyline, and
- treating voids as a result of trauma in a high risk patient with the subject composition containing an antibiotic (an example would be a long procedure involving an open fracture where the patient is immune compromised),
- treating of osteomyelitis,
- coating of orthopedic implants and other in-dwelling medical devices,
- filling bone graft source sites with the subject composition containing a local anesthetic, such as bupivacaine, and
- prophylactic delivery of antibiotic in septic revisions and high-risk trauma cases, and therapeutic use in septic revisions of total joint prostheses.

A synthetic bone substitute has the advantage that it is of non-biological origin. The risk of contamination from allograft bone is eliminated when using synthetic bone substitutes.

Autograft bone usually comes from the patient's ileac crest. The source site is often painful for weeks after the procedure. The invention includes filling bone graft source sites with the subject composition containing a local anesthetic.

Demineralized bone matrix (DBM) alone can be added to the composition of the invention. DBM is decalcified bone that is a powder and is osteogenic. The DBM can be used in place of the inorganic salt component of the composition to the extent from 10-100%. In addition to or in place of DBM osteogenic agents may be included. Among the types of osteogenic agents that are appropriate are proteins, peptides, and small molecules that are non-peptidyl in nature.

Another category of applications is coatings. The compositions can be used to coat orthopedic implants and other in-dwelling medical devices (such as to coat stainless steel surgical plates with screw holes, femoral stems, pins, spacers, pumps and stents). The plates can be dipped, painted or sprayed with an antibiotic (and/or other bioactive agent) containing

composition. After application of the coating the non-aqueous solvent in allowed to evaporate. Curing can be affected in situ or by exposure to high humidity.

Delivery of bioactive agents in therapeutic or preventative applications other than orthopedics

Antibiotics, local anesthetics, osteogenic factors, anti-tumor agents and growth factors are examples of bioactive agents that can be delivered with the compositions of the invention. Drugs that act systemically are also amenable to delivery by the subject invention in the form of a depot (s.c. or i.m.).

Examples of bioactive agents include analgesics, anti-emetics, anti-depressants, hormones, vaccine antigens, in therapeutic or preventative applications other than orthopedics. Includes The subject invention includes sustained vaccine antigen delivery, delivery of antibiotic to a site of localized infection, intra-tumoral delivery of an anti-neoplastic drug, plus subcutaneous depots of a wide range of bioactive substances.

Medicinals (both non-protein drugs and medicinal proteins) useful with the compositions of the invention are presented in commonly owned US Patent 6,630,486, WO 99/15150 and U.S. Ser. No. 09/703,710 each of which is hereby incorporated by reference. Therapeutics, antigens, antibodies including monoclonal antibodies, adjuvants, and regulatory molecules such as hormones exemplify bioactive agents with medical applications.

Various anti-infectives useful in conjunction with the formulations of the invention include gentamicin, clarithromycin, doxycycline, minocycline, clindamycin, lincomycin, amikacin, penicillin, cefazolin, ciprofloxacin, enrofloxacin, norfloxacin, ofloxacin, silver sulfadiazine, imipenem, piperacillin, nafcillin, cephalexin, ceftiofur, cefoperazone, vancomycin, tobramycin, nystatin, and amphotericin B or salts thereof (e.g., pamoate salt). Forming the pamoate (a complexing agent) of these anti-infectives to form complexes such as amikacin pamoate, clindamycin and gentamicin pamoate, are useful in the formulations of the invention.

Cisplatin, paclitaxel, 5-FU, doxorubicin and other anti-neoplastic agents, can be delivered locally as described herein. In one embodiment, localized administration is beneficial in that systemic toxicity is reduced/eliminated but concentrations in the area of cancerous tissue are high. The anti-neoplastic agent can be directly administered to the tumor, for example, on the spine.

Vaccine antigens can be delivered with the system of the invention, for example, by injection(s.c. or i.m. injection). The system of the invention can also be used to deliver DNA and RNA.

Kit Systems for Preparation and Administration

It is convenient and advantageous to employ a kit comprised of dual compartments or containers (for example, dual syringes) in the use of the compositions of the invention. It this embodiment, the dry powder and liquid components are stored separately in respective moisture-proof compartments or containers (e.g., syringes). In many cases medicinals are more stable when stored dry. In a preferred embodiment, the powder (calcium salts, EF mixture, medicinal) is preferably contained in the moisture-free barrel of a sealed syringe #1, while the liquid polymer solution is contained in a moisture-free barrel of a sealed syringe # 2. The two syringes may be fluid-connected, for example by means of male and female connectors associated with respective ones of the syringes or by means a separate Leur lock connector. The liquid phase of syringe #2 may then be injected into the powder phase of syringe #1. Mixing and dissolution are achieved by reciprocal action for a sufficient number of cycles, for example about 40 cycles. After removal of one syringe (empty) the air is removed and the composition is installed through an attached needle or cannula.

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The following Examples are illustrative, but not limiting of the compositions and methods of the present invention. Other suitable modifications and adaptations of a variety of conditions and parameters normally encountered which are obvious to those skilled in the art are within the spirit and scope of this invention.

EXAMPLES

Abbreviations:

-CP = calcium phosphate mixture which includes aTCP(60%), $CaHPO_4$(25%), $CaCO_3$(9)%), HA(2%), and Na_2HPO_4(4%)

-6%EC/NMP = 6% Ethyl cellulose (Sigma Chemical product number E-8003) in dry N-methylpyrrolidone (w/v).

-CSCast = calcium sulfate-hemihydrate/calcium stearate (95/5,wt/wt)

-EF(1) mixture = effervescent mixture = 3.7g adipic acid + 4.2g $NaHCO_3$

-EF(2) mixture = effervescent mixture 1.51g $AlNH_4(SO_4)_2$-$12H_2O$ + 0.84g $NaHCO_3$

-PBS = phosphate buffered saline (10mM phosphate buffer-pH 7.4, 2.7mM KCl, 13.7 mM NaCl)

Example 1

Preparation of non-aqueous amikacin calcium phosphate cement

Amikacin sulfate (50mg) was ground and added to 1g of CP mixture. EC/NMP (600μl, 6%) was added to this powder and blended for 1 minute. This suspension was transferred into a 1ml syringe and injected into a cylindrical mold, 12 mm by 6mm . The disc sample was placed in a glass vial containing 10ml of PBS buffer. The vial was incubated at 37° C and at 24 hr intervals the buffer was removed for testing and fresh buffer was added. The samples containing eluted drug were analyzed microbiologically. The amount of drug in the eluate was calculated from a standard curve.

Release profile CP Amikacin Cement

Day	% Released
1	13
2	11
3	10
4	10
5	5
6	5
7	7
8	7

Example 2

Preparation of non-aqueous enrofloxacin calcium phosphate cement

Enrofloxacin (50mg) was ground and added to1g of the CP mixture. This mixture was then combined with the EC/NMP (600μl, 6%) solutions and mixed for 30 seconds. The slurry was transferred into a 1ml syringe and injected into a cylindrical mold, 12 mm x 6mm. The disc sample was placed in a glass vial containing 10ml of PBS buffer and incubated at 37° C.

Buffer was changed at 24 hour intervals and analyzed microbiologically. The amount of drug in the eluate was calculated from a standard curve.

Release profile (2)

Day	% Released
1	20
2	17

3	17
4	5
5	2
6	2
7	2
8	2
9	2
10	2
11	2

Example 3

Preparation of non-aqueous enrofloxacin calcium sulfate cement

Enrofloxacin (50mg) was ground and mixed with 1g CSCast. EC/NMP (600μl, 6%) was added to the dry mixture and mixed for 30 seconds. The slurry was loaded into a 1ml syringe and injected into a cylindrical mold,12 mm by 6mm. Disc was placed in a glass vial containing 10ml of PBS buffer. The vial was incubated at 37° C and the buffer changed at 24 hr intervals. Supernatant was analyzed microbiologically. The amount of drug in the eluate was calculated from a standard curve.

Release profile (3)

Day	% Released
1	30
2	17
3	11
4	2
5	2

Example 4

Preparation of non-aqueous bupivacaine calcium phosphate cement

Bupivacaine HCl (50mg) was ground and mixed with 1g of CP. EC/NMP (600μl, 6%) was added to the dry mixture and blended for 30 seconds. The suspension was transferred into a 1ml syringe and injected into a cylindrical mold, 12 mm by 6mm. The disc was placed in a glass vial containing 10ml of PBS buffer. The vial was incubated at 37° C and the buffer was changed at 24 hr intervals. Drug concentration in the samples was determined spectrophotometrically (260nm).

Release profile (4)

Day	% Released
1	12
2	7
3	5
4	5
5	5
6	3
7	3
8	3
9	3
10	3

Example 5

Preparation of nonaqueous bupivacaine calcium sulfate cement

Bupivacaine HCl (50mg) was ground and mixed with 1g CSCast. EC/NMP (600μl, 6%) was added to the dry mixture and blended for 30 seconds. The slurry was loaded into a 1ml syringe and injected into a cylindrical mold, 12 mm by 6mm. The disc was placed in a glass vial containing 10ml of PBS. The vial was incubated at 37° C and the buffer was changed at 24 hr intervals. Drug concentrations in the eluate were determined spectrophotometrically at 260nm.

Release profile (5)

Day	% Released
1	47
2	16
3	6
4	3
5	1
6	1

Example 6

Preparation of nonaqueous vancomycin calcium phosphate cement

Vancomycin-HCl (50mg) was ground and mixed with 1g of CP. EC/NMP (600μl, 6%) was added to the dry mixture and blended for 30 seconds. The slurry was transferred into a 1ml syringe and injected into a cylindrical mold, 12 mm by 6mm.

The disc was placed in a glass vial containing 10ml of PBS buffer and incubated at 37°C. The buffer was replaced at 24 hr intervals. Drug concentration in samples was determined spectrophotometrically at 280nm.

Release profile (6)

Day	% Released
1	25
2	8
3	5
4	4
5	4
6	2

Example 7

Preparation of non-aqueous vancomycin calcium sulfate cement

Vancomycin-HCl (50mg) was ground and mixed with 1g CsCast. EC/NMP (600μl, 6%) was added to the dry mixture and mixed for 30 seconds. The slurry was transferred into a 1ml syringe and injected into a cylindrical mold, 12 mm by 6mm. The disc was placed in a glass vial containing 10ml of PBS buffer and incubated at 37° C. The buffer was changed at 24 hr intervals. Drug concentration in samples was determined spectrophotometrically at 280nm.

Release profile (7)

Day	% Released
1	47
2	20
3	7
4	4
5	3
6	2

Example 8

Preparation of non-aqueous calcium sulfate porous cement

CSCast (900mg) and 100mg of EF(1)mixture were mixed. EC/NMP (600μl, 6%) was added to the dry mixture and blended for 30 seconds. The slurry was loaded into a 1ml syringe and injected into a glass vial containing 3ml of PBS buffer. The suspension solidified instantly and evolution of carbon dioxide was observed. The material was allowed to solidify in the buffer at room temperature for 24 hrs.

Example 9

Preparation of non-aqueous calcium sulfate porous (ammonium alum) cement

CSCast (900mg) and 100mg of EF(2)mixture were blended. EC/NMP (600μl, 6%) was added and the combined powders were mixed for 30 seconds. When injected into PBS at room temperature or at 37 C, the suspension solidified immediately. The resulting solid gave off carbon dioxide. Similar results were observed with ammonium aluminum sulfate.

Example 10

Preparation of non-aqueous calcium phosphate porous cement

CP mixture (930mg) and 70mg of EF(1)mixture was combined. EC/NMP (600μl, 6%) was added to the dry mixture and mixed for 30 seconds. The slurry was transferred into a 1ml syringe and injected into a glass vial containing PBS buffer. The liquid solidified instantly and carbon dioxide was released. Similar results were observed with other effervescent mixtures over a range of concentrations up 15% based on the weight of the CP mixture.

Example 11

Coating of implants

Formulations A and B were used to coat stainless steel surgical plates with screw holes. The plates can be dipped, painted or sprayed. The solvent was allowed to evaporate overnight. The coated plate is cured by exposure to high humidity or used directly. In the latter case the curing is affected in situ.

Formulation A: CS/Cast (1g) plus EC/NMP (1ml) plus antibiotic up to 100 mg

Formulation B: CP (1g) plus EC/NMP (1ml) plus antibiotic up to 100 mg

Example 12

Dual Syringe System

A finely ground powder consisting of calcium sulfate hemihydrate (930mg), amikacin sulfate (50mg) and EF 1 (70mg) is placed in a 5ml syringe (#1) fitted with a Luer lock. About 1ml is occupied by air. In syringe #2 (5ml also) is contained 800ul of 6% EC in NMP. The syringes are coupled via a Luer lock connector. With the syringes horizontal, the plunger of syringe #2 is pushed to expel the liquid into syringe # 1. The plunger of syringe #2 is retracted to recover the liquid, which now contains some suspended solid. The process is repeated three

times using just the plunger of syringe # 2. Both plungers are then depressed in turn to the extent of 40 cycles back and forth, which produces a smooth, homogeneous suspension.

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It will be readily apparent to those skilled in the art that numerous modifications and additions may be made to the present invention, the disclosed device, and the related system without departing from the invention disclosed.